ACTA ONCOLOGICA
2021, VOL. 60, NO. 5, 649–652
https://doi.org/10.1080/0284186X.2021.1887516

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LETTER TO THE EDITOR

Thymic malignancies treated with active scanning proton beam radiation and Monte Carlo planning: early clinical experience

Mary McGunigal[a], Marc Margolis[b], Matthew Forsthoefel[a], Tanvee Singh[c], Katherine Amarell[c], David Deblois[a], Lloyd Campbell[a], Chul Kim[d], Stephen Liu[d], Peter J. Bergquist[e], Pedro Debrito[f], Brian T. Collins[a], Giuseppe Giaccone[g] and Jonathan W. Lischalk[h]

[a]Department of Radiation Medicine, Georgetown University Hospital, Washington, DC, USA; [b]Division of Thoracic and Esophageal Surgery, Department of Surgery, Georgetown University Hospital, Washington, DC, USA; [c]Georgetown University School of Medicine, Washington, DC, USA; [d]Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Hospital, Washington, DC, USA; [e]Department of Radiology, Georgetown University Hospital, Washington, DC, USA; [f]Department of Pathology, Georgetown University Hospital, Washington, DC, USA; [g]Department of Oncology, Weill Cornell Medical Center, New York, NY, USA; [h]Department of Radiation Oncology, Perlmutter Cancer Center at New York University Winthrop Hospital, New York, NY, USA

ARTICLE HISTORY Received 7 January 2021; Accepted 3 February 2021

Background

Thymoma and thymic carcinoma are rare neoplasms of the anterior mediastinum [1]. They are managed with upfront surgical resection, if feasible, followed by adjuvant recommendations dictated primarily by the completeness of the resection and pathology. Adjuvant therapy remains an area of controversy in the management of thymic malignancies given the rarity of the disease and the few, small prospective studies available to guide decision-making. There is debate regarding the benefit of postoperative radiotherapy in the setting of early stage, completely resected thymoma (particularly stage II, which has an indolent course and uncommon recurrences) and thymic carcinoma as the data is mixed in regard to local control and survival benefits seen in this setting [2–5].

However, more modern radiation techniques including intensity-modulated radiation therapy (IMRT) and proton beam radiotherapy (PBT), have allowed for significant dose reductions to the normal structures of the mediastinum including the heart and lungs. In particular, PBT has demonstrated a physical dose superiority in comparison to X-rays due to the 'Bragg Peak' which eliminates exit dose and reduces integral dose. This can be particularly beneficial in treating tumors of the anterior mediastinum where critical organs at risk (OAR) lie just beyond the prescribed dose [6]. Mediastinal radiation carries risk of both acute and long-term toxicities ranging from cardiac toxicities (e.g. pericarditis, congestive heart failure, valvular disease, and coronary artery disease) to pulmonary toxicities (pneumonitis, fibrosis, etc.) and esophagitis [7–10].

While the dosimetric benefits of reducing radiation exposure to OARs with PBT are well documented, there is a paucity of literature comparing proton dosimetry to X-ray-based thoracic radiation for thymic malignancies. Additionally, most studies to date utilizing PBT for thymoma have implemented pencil beam scanning (PBS) dose calculation algorithms. This study is particularly novel as we are the first institution to publish clinical data on patients with thymic malignancies treated with PBT and calculated using Monte Carlo-based planning. Here, we report dosimetric comparisons and short-term clinical outcomes of these rarely seen malignancies using modern PBS-PBT at one of the first single-room PBS centers in the United States.

Material and methods

Patient eligibility

This single institutional review of patients treated for thymic malignancies (thymoma or thymic carcinoma) was approved by the local Institutional Review Board (0000-1269). All patients were evaluated by a multidisciplinary thoracic oncology team. Patients were staged utilizing the AJCC 8th edition and Masaoka staging systems.

Simulation and contouring

All patients underwent computed tomography (CT)-based simulation with accompanied 4-dimensional computed tomography (4D-CT) for assessment of respiratory motion (GE LightSpeed RT16). Gross tumor volume (GTV) was contoured based on preoperative imaging fused with planning scans and adjusted according to anatomical shifting of the lung and mediastinal structures following surgical resection to help create the clinical target volume (CTV). OAR were contoured and included lung, heart, breasts, esophagus, thyroid, spinal cord, and skin (3 mm).

CONTACT Jonathan W. Lischalk jonathan.lischalk@nyulangone.org Department of Radiation Oncology, Perlmutter Cancer Center at New York University Winthrop Hospital, 150 Amsterdam Ave, New York, NY10023, USA

Treatment planning and delivery

Dose calculations and planning optimization were performed on the average phase of the simulation 4D-CT. Proton plans were generated utilizing RayStation version 8 A with Monte Carlo planning (RaySearch Laboratories, Stockholm, Sweden).

Follow-up

Patients were seen on a weekly basis for on treatment visits and acute toxicity was defined as that occurring within 90 days of treatment completion to include the first patient follow-up following RT completion. Late toxicity was defined as that occurring greater than 90 days after completion of radiotherapy. Toxicity was reported using the Common Terminology Criteria for Adverse Events version 5.0 (CTACE v5.0). Patients were followed by serial CT scans of the chest and clinical examination at 3-month intervals for the first year and subsequently every 6–12 months thereafter. All patients were referred to cardiology for baseline evaluation and cardiac care optimization.

Statistical analysis

Comparison plans with 3D-CRT, IMRT, PBT with PBS dose calculation algorithms, and PBT with MC dose calculation algorithms were generated for each patient. The means of all dosimetric variables were calculated and compared using ANOVA. Analyses were performed using Statistical Package for the Social Sciences (SPSS) version 24 (Armonk, NY).

Results

Seven patients were treated with adjuvant proton beam radiation from 2018 to 2019 save for one patient whose surgery was aborted and was treated definitively. All patients had positive margins (R1 or R2 resection) as an indication for adjuvant radiation. Six of these were thymoma patients, and one patient with thymic carcinoma. Patients were treated to median dose of 54 Gy after definitive resection. Median age was 69 (range 17–78). Masaoka stage ranged from I to IVA.

Compared with X-ray plans (both 3D and IMRT), PBT was associated with nominally lower mean doses to both the esophagus and heart, although not statistically significant (see Table 1). Mean doses to the esophagus in Gy were 13.74 [3D] versus 17.01 [IMRT] versus 11.39 [PBS] and 11.68 [MC]; $p = .437$) and for mean heart doses, 17.42 [3D] versus 16.75 [IMRT] versus 14.46 [PBS] versus 15.13 [MC], $p = .669$ (Table 1).

Proton plans demonstrated a statistically significant lower mean and volumetric lung doses as well as a lower spinal cord maximum dose as compared to X-rays. Mean lung doses in Gy were: 12.35 [3D] versus 12.48 [IMRT] versus 7.69 [PBS] versus 8.83 [MC], $p < .01$. Of note, mean lung dose along with lung V20 have both been established as dose-volume histogram parameters predictive of risk of pneumonitis in patients who receive mediastinal radiation [11]. In addition to having statistically significantly lower mean lung dose, proton plans also had a significantly lower lung V20. Target volume coverage was lowest in the 3D plans, with a mean coverage of 65.8% (vs. >90% for the IMRT and proton plans).

With regards to acute toxicity, two patients developed grade 2 radiation dermatitis (Table 2). Otherwise, no patients developed any other grade 2 or higher acute toxicity during PBT. No patient has reported additional acute toxicities. Additionally, no patient has developed any evidence of local, regional, or distant progression. Median follow-up was 21 months.

Discussion

This is the first investigation to report dosimetric and clinical outcomes of PBS-PBT implementing Monte Carlo dose calculations for the treatment of thymic malignancies. Historically, the majority of proton therapy centers employ a PBS algorithm for dose calculations, with Monte Carlo-based treatment planning currently rarely used in clinical practice [12]. PBS delivery systems use an electronically guided scanning system to deliver treatment *via* numerous 'spots' (of high energy protons); scanning magnets adjust the pencil beams' position to effectively sweep protons across a target volume laterally with energy adjustments delivering spots along isoenergetic layers.

We demonstrate excellent target volume coverage with dramatically lower radiation exposures of OARs, particularly heart and lungs, relative to comparison IMRT plans. Though our cohort is relatively small, existing literature on the role of proton therapy in thymic malignancies is quite sparse, comprised of two retrospective studies smaller than our cohort (4 and 6 patients) and two larger more heterogeneous studies (22 and 27 patients) [13–16]. Vogel *et al.* in 2016 presented the first prospective cohort of patients with thymic malignancies treated using a passive scatter proton therapy treatment system; 27 patients were treated utilizing double scatter PBT in the adjuvant, definitive, and salvage settings [15]. As in our study, they observed no grade 3 or higher treatment-related toxicities and acute toxicities were predominantly limited to dermatitis. Averaged across the entire cohort, exceptionally low dosimetric parameters were observed including mean doses of lung, heart, and esophagus at 9.4, 9.6, and 9.7 Gy, respectively. In a study of adjuvant PBT in a sample of four thymoma patients, Parikh *et al.* reported statistically significant reduction in mean heart, lung and esophagus doses as compared to X-rays. Mean doses to the heart, esophagus and lungs from the PBT (PBS and MC based) plans in our study were in line with mean doses from prior similar studies [16].

Long-term follow-up and larger numbers of this uncommon patient population are needed to enhance understanding of how dosimetric benefits may translate clinically. The Vogel study reported 100% local control rate among 27 patients at a median follow-up at 2 years, and 3-year regional control of 96% and 3-year OS of 94%. Our own preliminary results thus far are promising as there were no high-grade acute toxicities, no instances of subacute toxicity aside from 1 case of grade 1 pneumonitis, and no recurrences to date.

Table 1. Dosimetric characteristics.

	Mean in 3D plan	Mean in IMRT plan	Mean in PBT plan (PBS)	Mean in PBT plan (MC)	*p*-Value (statistically significant in bold)
PTV V100% (%)	65.8	94.6	94.19	90.6	**.000363**
Esophagus mean (Gy)	13.74	17.01	11.39	11.68	.437
Esophagus V50Gy (%)	2.6	0.2	2.2	1.9	.736
Heart mean (Gy)	17.42	16.75	14.46	15.13	.669
Heart V45Gy (%)	15.5	13.0	14.0	14.7	.769
LAD mean (Gy)	34.45	29.55	27.97	29.15	.836
Skin max (Gy)	47.15	36.59	49.96	48.69	**.012**
Spinal cord max (Gy)	18.12	32.53	9.24	10.93	**.000341**
Lung mean (Gy)	12.35	12.48	7.69	8.83	**.0009**
Lung V20Gy (%)	23.9	21.0	14.3	16.3	**.000274**
Lung V5Gy (%)	44.1	60.7	28.1	32.2	**.00004**
LV mean (Gy)	12.19	8.59	6.67	6.88	.368
LV 20 Gy (%)	22.1	11.2	11.8	12.9	.403

Table 2. Acute toxicity outcomes.

	Grade 1	Grade 2
Radiation dermatitis	1	1
Skin hyperpigmentation	5	2
Cough	0	0
Pleural effusion	0	0
Pneumonitis	1	0
Pleuritic pain	0	0
Shortness of breath	0	0
Esophagitis	1	0
Weight loss	0	0
Anorexia	0	0
Fatigue	3	0
Chest wall pain	2	0

In other prior studies, rates of pneumonitis were similarly low [17,18].

Treatment of thoracic malignancies presents technical challenges due to respiratory motion and tissue heterogeneity that require proper optimization during planning. Our use of Monte Carlo dose calculations in large part explains the variations of OAR dosimetry from prior publications. This is consistent with prior dosimetric studies which have also shown that MC dose calculations offered realistic dose calculations as compared to PBS-based planning particularly in more heterogeneous tissue such as the thorax [19,20].

Although thymic malignancies are rare, given the location and patient population, long-term toxicity associated with low and intermediate doses of radiation can have a more profound impact. Our small study underscores this as it includes patients as young as 17 and 31 who were otherwise in excellent health. The rarity of these tumors has historically been a barrier to implementing large-scale phase III randomized trials however there are two currently underway in China—years from completion—examining the role of post-operative radiation therapy in Stage II–III thymoma [21,22]

Prior studies on proton therapy for thymic malignancies have reported on three-dimensional conformal double-scattered proton therapy and more recently, pencil-beam scanned therapy, which has been corroborated in other cancers to have improved sparing of OARs over passive scatter techniques, particularly proximal to the target [23]. In our study, when MC plans were compared to PBS plans, there was a reduction in PTV coverage, suggesting that PBS calculation may lead to less realistic dose calculations, leading to under-coverage of the target if optimization algorithms are not utilized. These results are in line with prior findings that MC-based algorithms may be more suitable for thoracic tumors treated with protons [19].

Study limitations include the small and relatively heterogeneous patient cohort, a function of the rarity of this disease, and lack of long-term follow-up. However, our dosimetric results utilizing MC planning and optimization for the thymic tumors treated with PBS-PBT are the first to be reported based on review of existing literature. Prior publications have advocated for the routine use of MC planning for thoracic cases being treated with active scanning proton therapy systems including lung cancer and mediastinal lymphoma cases [19,24]. This is the first study of its kind to do so in the setting of thymic malignancies. A barrier to the more widespread adoption of MC-based planning historically has been the increased computation time; however, with ongoing advances in software to expedite planning, this will likely be of lesser concern in the future [16]. Given the decreased dose to OARs as well as the improved accuracy of dose distributions in thoracic malignancies provided by Monte Carlo calculation algorithms, increased integration into clinical practice is expected [19].

Conclusion

Radiotherapy has an established role in the management of thymic malignancies [18,25]. Proton beam therapy has emerged as an ideal modality for thymic malignancies given its ability to minimize toxicity in this rare cohort with prolonged survivorship. Our results demonstrate the dosimetric benefits of protons over X-rays in the treatment of thymic malignancies with minimal acute toxicity while maintaining acceptable coverage. This study is particularly unique as treatment was calculated and delivered using Monte Carlo-based planning. To date, there are no reports of MC-based proton therapy for thymoma in the literature. Our results are in line with prior findings that MC-based algorithms may be more suitable for thoracic tumors. We advocate for the consideration of proton therapy over X-rays for the treatment of thymoma and thymic carcinoma. We also recommend the use of MC-based algorithms. Longer-term follow-up is critical as toxicity and local control rates are monitored in these patients.

Acknowledgments

Thanks to Elizabeth Ballew for contributing to the data collection and development and maintenance of the institutional review board for this study, and our chairman Dr. Anatoly Dritchshilo for his general support and guidance.

Disclosure statement

Dr. Lischalk and Dr. Collins are paid speakers for Accuray. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ORCID

Mary McGunigal http://orcid.org/0000-0002-6264-144X
Matthew Forsthoefel http://orcid.org/0000-0001-6813-6121

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